PCT/EP 99/06166

09/763602

EP99/0616

REC'D 19 NOV 1999

WIPO PCT

EJU

PA 140209

# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 18, 1999

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

BEST AVAILABLE COPY

APPLICATION NUMBER: *09/141,781*

FILING DATE: *August 27, 1998*

**PRIORITY DOCUMENT**

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PATENT AND TRADEMARK OFFICE UNITED STATES OF AMERICA

By Authority of the

COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. Jackson

H. L. JACKSON

Certifying Officer

# ASCORBATE-ISOQUERCETIN COMPOSITIONS

The present invention relates to novel compositions containing ascorbic acid with an increased bioavailability of this vitamin. These compositions are useful as food supplements possessing preventive properties against damage to human tissues, including skin cells due to oxidative stress.

## Background of the Invention

In vivo ascorbic acid (vitamin C) exists in three forms:

a) as an ascorbate in form of an ascorbate monoanion,
b) as the reversibly oxidized form of a free radical, called semidehydroascorbic acid which could be reversibly oxidized to dehydroascorbic acid or reversibly reduced to ascorbate monoanion, and
c) as dehydroascorbic acid (oxidized form of semidehydroascorbic acid).

Only ascorbate possesses specific vitamin C activity: as a cofactor for enzymes. Observed physiological activities of semidehydroascorbic acid and dehydroascorbic acid formed in vivo from ascorbate are considered to be based on their reversible reductions to ascorbates. See Buettner GR (1993), The pecking order of free radicals and antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate, Arch. Biochem. Biophys. 300, 535543; Dhariwal KR, Black CD, Levine M (1991), Semihydroascorbic acid as an intermediate in norepinephrine biosynthesis in chromaffin granules. J. Biol. Chem. 266, 12908-12914; Washko P. W., Wang Y., Levine M. (1993), Ascorbic acid recycling in human neutrophils, J. Biol. Chem. 268, 15531-15535; and Welch R. W., Wang Y., Crossman A. Jr., et al. (1995), Accumulation of vitamin C (ascorbate) and its

oxidized metabolite dehydroascorbic acid occurs by separate mechanisms, J. Biol. Chem. 270, 12584-12592.

The second form of ascorbic acid, semidehydroascorbic acid (ascorbate free radical), participates in univalent redox systems that are in the antioxidant defense activity. See Bors, W., Michel, Ch., Schikora, S., (1995), Interaction of Flavonoids with Ascorbate and Determination of their Univalent Redox Potentials: a Pulse Radiolysis Study, Free Radical Biology and Medicine, vol. 19, No. 1, 45 - 52. This means semidehydroascorbic acid participates most likely participates in free radical scavenging activities. According to the article Gordon, M. H. (1996), Dietary Antioxidants in Disease Prevention, Natural Product Reports, pp. 265 - 273, "ascorbate appears to be the most important non-protein antioxidant in plasma", p. 270. Ascorbic acid is absorbed from the gastrointestinal tract in the form of ascorbic acid. Dehydroascorbic acid is reduced to ascorbic acid for gastrointestinal absorptions, (Rose, R. C., J. L. Choi, and M. J. Koch, (1988), Intestinal transport and metabolism of oxidized ascorbic acid, Am. J. Physiol., 254, G824-G828).

Structures of body tissues are susceptible to damage caused by the oxidative stress, e.g., by the accumulation of reactive oxygen species during aging, chronic environmental stress, inflammations or general metabolic dysfunctions. The role of free radicals and reactive oxygen species in aetiology of human diseases (e.g. cancer, atherosclerosis, rheumatoid arthritis, inflammatory bowel diseases, immune system dysfunctions, brain function decline, connective tissue dysfunctions) is well established. See: Gordon, supra. Uncontrolled generation of free radicals, especially chronic exposure to reactive oxygen species leads to chronic intracellular damage, to oxidative stress and premature aging. Cells of the human body possess metabolic antioxidant defenses which are supported by dietary antioxidants. The early observations of the antioxidant defense metabolic processes involved vitamin C and flavonoids. See Bentsath A, Rusznyak St, Szent-Gyorgyi A. (1937), Vitamin P. Nature (London), 139, 326-327; Bezssonoff, N. (1926), Lafaiete antiscorbutique est-il du a deux substances differentes C.r. Acad. Sci., Paris 183, 1309-131 0; Bull. Soc. Chim. Biol.

(1927), 9, 568-579; Bentsath A, Rusznyak St, Szent-Gyorgyi A. (1936), Vitamin nature of flavones, Nature (London), 138, 798; and Blanc, B, and Von der Muehl, M. (1967), Interaction d'une flavonoide et vitamine C; son influence sur le poids du cobaye et le contenu en vitamine C de ses organs, Int. Z. VitaminForsch., 37, 156 - 169. Ascorbic acid is not only important non-protein antioxidant in human plasma (Gordon, supra), it increases the cytoprotective activities of quercetin and rutin. It has been shown, for instance, that quercetin protects connective tissue and specifically skin cells (e.g. fibroblasts, keratinocytes, and endothelial cells) from this type of damage. See Skaper et al. 1997. A protective effect of flavonols on the cardiovascular and nervous systems and their role as chemoprotective agents in carcinogenesis has been demonstrated.

Oxidation of the ascorbate in the human body by xenobiotics often leads to the accumulation of semidehydroascorbic acid or dehydroascorbic acid in organs where these forms interfere with the regular metabolism. As ascorbate is a cofactor for eight isolated enzymes (carrying out collagen synthesis, carnation synthesis, peptide admiration, tyrosine metabolism, and catecholamine synthesis) the decrease of the concentration of ascorbate in body tissues and fluids may lead to serious metabolic dysfunctions.

The possibilities of protecting ascorbic acid in vivo were based on very early observations of Bentsath et al. (1936 and 1937), supra, that the ascorbic acid activity in humans and guinea pigs is intensified by the great group of "vegetable dyes, the flavones or flavonols". It has been known that flavonoids are contributing to the maintenance of the concentration of the administered ascorbate in adrenal, kidneys, spleen, and the liver of the organisms investigated and improve the antiscorbutic effect of the dosages of ascorbate used. See Papageorge, E. and Mitchell, G. L. (1949), The effect of oral administration of rutin on blood, liver and adrenal ascorbic acid and on liver and adrenal cholesterol in guinea pigs, J. Nutr. 37, 531 - 540; Cotereau, H., Gabe M., Gero, E., Parrot, J. L.(1948) Influence of Vitamin P (C2) Upon the amount of ascorbic acid in the organs of the guinea pig, Nature, 161, 557-558; Crampton, E. W. and Lloyd, L. E. (1950), A qualitative estimation of the effect of rutin on the biological potency of vitamin

C, J. Nutr., 41, 487 - 498; Douglas, C. D. and Kamp, G. H. (1959), The effect of orally administered rutin on the adrenal ascorbic acid level in guinea pigs, J. Nutr., 67, 531 - 536; Blanc, B, and Von der Muehl, M. (1967), Interaction d'une flavonoide et vitamine C; son influence sur le poids du cobaye et le contenu en vitamine C de ses organs, Int. Z. VitaminForsch., 37, 156 - 169; supra, and Zloch, Z. (1973), Inflows von Bioflavonoids auf den Vitamin-C-Wert Kristal liner Dehydroascorbinsaeure Int. J. Vit. Nutr. Res. 43, 378 - 386.

The mechanism of this effect, called "the vitamin C-economizing function" of some flavonoids ("facteur d'economie de L'acide ascorbique" of Bezssonoff, 1926 and 1927, supra) has been recognized in many laboratories. For example, it was found that, among flavonoids tested, flavonols the have strongest ability to inhibit ascorbic acid oxidation in near neutral solutions (pH 5 - 7). See Harper, K. A. Morton, A. D. and Rolfe, E. J. (1969), Phenolic compounds of black currant juice and their protective effect on ascorbic acid. III Mechanism of ascorbic acid oxidation and its inhibition by flavonoids. J. Food Tech., 4, 255 - 267) 1969. Harper et al. also pointed out that the presence of free hydroxyl groups at carbon atoms 3, 7, 3', and 4' in a flavonol molecule improves the antioxidative effect of the flavonol molecule, this means, it inhibits ascorbate oxidation more effectively.

But there was neither an effective method nor a useful orally applicable formulation leading to an increased level of active ascorbate in human tissue.

Accordingly, there was a need for a composition useful for the protection of the orally administered ascorbic acid and enhancement of vitamin activity in the tissues.

Now it has been found that isoquercetin effectively inhibits ascorbate oxidation. The maintenance of the reduced form of ascorbic acid by isoquercetin maintains the ascorbic acid level in body tissues and fluids.

This effect perhaps may be explained in that isoquercetin not only shows three free hydroxyl groups mentioned by Harper et al. (supra), more specifically, hydroxyl groups attached to carbon atoms 7, 3', and 4', but also a glucopyranoside moiety with an

additional four free hydroxyl groups 0-attached to the carbon 3 of isoquercetin. Therefore, the increased effectiveness of ascorbate protection may be caused by the fact that isoquercetin contains a glucose molecule. This glucose molecule seems to be the reason why isoquercetin is able to use the sodium-dependent glucose transport pathway of the intestinal brush-border membrane in its absorption process (Gee, J. M. M.S. DuPont, M.J.C. Rhodes, and Ian T. Johnson, Quercetin glucosides interact with the intestinal glucose transport pathway, Free Radical Biology and Medicine, 25, (1), 19 – 25, 1998). Experiments have also shown that the absorption of isoquercetin is better than that of pure aglycone.

Earlier pharmacokinetic studies with isoquercetin were consistent with the results obtained and explained by Gee at al., supra, by having shown excellent absorption rate and bioavailability of isoquercetin (Hollman and Katan, 1997, Determinants of the absorption of the dietary flavonoid quercitin in man, Proefschrift. 1997, Universiteit Nijmegen).

It has been found that ascorbate is not only able to regenerate oxidized flavonols by reducing them, (Yamasaki, H., Sakihama Y., Ikehara, N. (1997), Flavonoid-peroxidase reaction as a detoxification mechanism of plant cells against H202, Plant Physiology, 115, 1405 1412) but also to protect quercetin (aglycone of the isoquercetin) against oxidative degradation and to maintain the antiviral properties of quercetins. See Vrijsen, R., Everaert L., Boeye, A. (1988), Antiviral activity of flavones and potentiation by ascorbate. Journal of General Virology, 69, 1749 - 1752.

This means, there is a synergistic effect between isoquercetin and ascorbate in human tissue leading to higher effectiveness of both, ascorbate and isoquercetin.

For isoquercetin these activities are as follows:

it has shown antihypertensive properties,

(Kameda, K., Takaku, T., Okuda, H., Kimura, Y., Okuda, T., Hatano T., Agata, 1. And Arichi, S. (1987), Inhibitory effects of various flavonoids isolated from

leaves of persimmon on angiotensin-converting enzyme activity, J. Nat. Prod., 50, 680 - 683);

it inhibits the biosynthesis and release of prostaglandin-like substances, (Chanh P.H., lfansyyah, N., Chahine, R., Mounayar-Chalfou, A., Gleye, J. and Moulis, C. (1986), Comparative effects of total flavonoids extracted from Ribes nigrum leaves, rutin and isoquercitrin on biosynthesis and release of prostaglandins in the ex vivo rabbit heart, Prostaglandins 1. Med., 22, 295-300);

it produces dose-dependent protection in oxidative DNA damage, (Noroozi, M., W. J. Angerson, M.E.J. Lean (1998), Effects of flavonoids and vitamin C on oxidative DNA damage to human lymphocytes, American Journal for Clinical Nutrition, 67, 1210 – 1218);

it possesses preventive properties against damages of vascular and connective tissues (especially skin); and

it is therapeutically useful in the treatment of dysfunctions of the digestive tract (Set, T., Yasuda, 1, and Akimbo, K. (1992), Purgative activity and principals of the fruits of Rosa multiflora and R. wichuraiana, Chem Pharm. Bull, (Tokyo) 40, 2080 2082).

Now we have found by experiments that the combination of vitamin C with the most easily bioavailable bioflavonoid, isoquercetin, is most effective in prevention of and in defense against stress dysfunctions, especially against oxidative damage of living tissues including brain, vascular and connective tissues (especially skin).

It has been found that a composition comprising ascorbic acid and one or more derivates of quercetin selected from the group quercetin-3-0-glucoside (isoquercetin), quercetin-4'-glucoside, quercetin-3'-glucoside and acid-quercetin-7-glucoside in a molar

ratio of ascorbate to flavonoid in the range of 2:1 to 1:2, preferably in the molar ratio of 1:1, orally administered, conveys in vivo: higher protection, longer maintenance of biological activity, higher concentration in tissues and higher biological efficiency to vitamin C in organs of the human body. This adduct also provides the properties of higher protection, longer maintenance of biological activity, higher concentration in tissues, and higher biological efficiency in organs of the human body to isoquercetin and the other glucosides of the above mentioned group.

Useful compositions may contain in a daily dose 30 - 1500 mg of an active amount of ascorbic acid or preferably of physiologically active ascorbate in the form of its sodium salt, calcium, other mineral, or organic cation salts in a daily dose. The compositions according to the present invention may be prepared in the form of tablets, capsules or syrups. These application forms may also contain further active ingredients in useful amounts like vitamins, suitable salts of Mg, Ca, K or Fe and perhaps trace elements.

The compositions of the present invention preferably are useful as food supplements, but they may also be administered in a pharmaceutical treatment.

The present invention makes available:

a) a method of maintaining long biological activity and a high concentration of ascorbate and isoquercetin in human organs (including skin), tissues and cells,

b) a method of protection against oxidative damage of human organs, tissues and skin cells,

c) a method of prevention of arteriosclerosis, cardiovascular diseases, and other damage to vascular tissues, of allergic and inflammatory disorders, of bacterial and viral infections, of metabolic dysfunctions involving oxidative damages e.g., premature aging,

d) a method of supporting pharmacological treatments of diseases and dysfunctions caused by oxidative damages,

by oral administration of a composition described above. Generally speaking, compositions that are applicable contain at least ascorbic acid or ascorbate or any other form of this vitamin that would in vivo yield ascorbate, or semidehydroascorbic acid, or dehydroascorbic acid and isoquercetin. The decision which further ingredients should be components of a composition useful in one of the above mentioned methods depends on the special indication. Usually, if the composition is administered as a way of protection or prevention, useful further ingredients may be further vitamins, salts of Mg, Ca, K, Fe and trace elements in known amounts as used in food supplements. Compositions useful in a method of supporting pharmacological treatments may differ from them.

The superiority of isoquercetin and ascorbate used in combination for the protection of human cells, tissues and organs from the oxidative stress is based on two properties of isoquercetin and of ascorbate. First, on the quick intestinal absorption of orally administered isoquercetin and of ascorbate, and on the rapid and simple passage of both compounds through cytomembranes of human organs; secondly, on the specificity of interaction of isoquercetin with ascorbate. Specifically, ascorbate maintains isoquercetin in its active oxidized state and isoquercetin maintains ascorbate in its enzymatically active reduced state.

On the basis of our research on the bioavailability and on redox properties of isoquercetin and ascorbate, it has been found that orally administered mixtures of isoquercetin and ascorbate are most effective in protecting the organs (including skin), tissues, and cells from the chronic intracellular oxidative damages.

The uptake of isoquercetin taken into the human body is caused by the sodium-dependent glucose transport system. This type of transport occurring in most animal species (Coady, M. J., Pajor, A. M., Wright, E. M. (1990), Sequence Homologies between Intestinal and renal Na(+)/glucose cotransporters. Am. J. Physiol. 259, C605 -

610) is active during the uptake of pyranosides as for example methyl alpha-D-glucopyranoside, (Hediger, M. A., Coady, M. J. Ikeda, T. S., Wright, E. M. (1987), Expression and Cloning and CDNA Sequencing of the Na(+)/glucose cotransporter, Nature, 330, 379 - 381). The sodium-dependent glucose transport system in mammals was studied in many laboratories. Koepsell and Spangenberg characterized Na(+)-D-glucose cotransport in the intestine (Koepsell H. and Spangenberg, J. (1994), Function and presumed molecular structure of Na(+)-D- glucose cotransport systems. J. Membr. Biol. 138 (1) 1 - 11). It is a cotransporting system composed of a set of two subunits: transport-mediating proteins and transport-modulating proteins. The first translocates the substrates and the second accelerates the $V_{max}$ of the Transport. The susceptibility of isoquercetin to be transported using the Na(+)-D-glucose cotransport is determined by the manner in which a non-glucose moiety is linked to glucose. More information about this is given in a review of Olson, A. L. and Pessin, J. E. (1996), Structure, function, and regulation of the mammalian facultative glucose transporter gene family, Annual Rev. of Nutrition, Vol. 16, 235 - 256. Direct evidence that isoquercetine uses a sodium-dependent glucose transport pathway of the intestinal brush-border membranes was obtained by Gee et al., supra.

Also the uptake of ascorbate in humans is caused by a sodium dependent glucose transport system. Interactions between glucose and ascorbate transport activity have been demonstrated in many tissues and cells. See Ramsey, S. C. and Levine, M. (1998) Absorption, Transport, and disposition of ascorbic acid in humans, Nutritional Biochemistry, 9, 116-130. Apparently ascorbate is absorbed in human intestine by a sodium-dependent active transport system, although in vitro about 10-20% of ascorbic acid moves into cells in the absence of sodium (Kuo, S.-M., More house, H. F., Lin, C.-P. (1997), Effect of antiproliferative flavonoids on ascorbic acid accumulation in human colon adenocarcinoma cells, Cancer Letters, 11, 131-137). The carrier proteins in the intestinal cell membranes bind and transport the vitamin across the membrane to its intracellular site of action. There are differences in transport kinetics, tissue specificity, $Na^+$-dependence and energy dependence (Ramsey and Levine, supra), but in most cases the transport of ascorbate is $Na^+$-dependent and requires metabolic energy. Kinetic

evidence suggests strongly that ascorbate may be transported by the same transporter as glucose and, therefore, by the same transporter as isoquercetin.

Pharmacokinetic studies with isoquercetin support the present invention as they show excellent absorption rate and bioavailability of isoquercetin. It is absorbed better than rutin and quercetin (Hollman, supra). Absorbed isoquercetin interacts with ascorbate protecting it and, at the same time, is being protected by ascorbate by being kept in the reduced state (Yamasaki et al., supra). It has also been shown that ascorbate protects quercetin (aglycone of the isoquercetin) against oxidative degradation and maintains quercetin's antiviral properties (Vrijsen et al., supra). Effectiveness of isoquercetin in interacting with ascorbate is strengthened by the fact that isoquercetin uses the preferential intestinal Na(+)-D-glucose cotransport discussed above.

Therefore, a most powerful dietary antioxidant composition is prepared using among other ingredients ascorbic acid and isoquercetin. The advantageous properties of these compositions are induced by the synergistic effect of isoquercetin protecting the activity of the orally administered ascorbic acid while maintaining its enzymatically active reduced form, and, on the other side, of ascorbate maintaining isoquercetin in its active oxidized state.

Surprisingly it was found that in contrast to other quercetin glucosides, isoquercetin shows far better absorption rates in the human intestinal tract than rutin or the quercetin aglycone and that it acts as a specific and most powerful dietary antioxidant at the same time.

This positive result was unexpected because mixtures of ascorbic acid and quercetin or quercetin glucosides other than isoquercetin were considerably less effective

.

A subject of this invention is that in humans the oral administration of a mixture or combination of ascorbic acid and isoquercetin (quercetin-3-0-glucoside); or of any of mixtures of ascorbic acid and quercetin-4'-glucoside; of ascorbic acid and quercetin-3'-glucoside; of ascorbic acid and quercetin-7-glucoside, with a suitable molar ratio,

preferably equimolar ratio, of ascorbate to flavonoid, conveys efficient protection against oxidative damages, due to long maintenance of biological activity of each of the ingredients and due to maintenance of high concentration of both ascorbate and isoquercetin in organs, tissues, and cells.

The invention of this application includes compositions containing the above mentioned ingredients useful for the prevention and treatment of atherosclerosis and other cardiovascular disorders, certain forms of cancer, allergic and inflammatory disorders, bacterial and viral infections, a number of metabolic dysfunctions, e.g., premature aging and other pathological conditions that involve oxidative damages.

The entire disclosure of all applications, patents and publications, cited above and below are hereby incorporated by reference.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

**WHAT IS CLAIMED:**

1. Orally applicable composition comprising ascorbic acid, ascorbate or a derivative of ascorbic acid or ascorbate in combination with one or more derivatives of quercetin selected from the group consisting of quercetin-3-O-glucoside (isoquercetin), quercetin-4'-glucoside, quercetin-3'-glucoside, and quercetin-7-glucoside.

2. Composition comprising isoquercetin in combination with ascorbic acid or a physiologically active ascorbate in the form of its sodium, calcium, other mineral or organic salts.

3. Composition according to claim 1 comprising a combination of (a) quercetin-3-o-glucoside (isoquercetin) or a mineral or organic salt thereof and (b) ascorbic acid, or a mineral or organic salt thereof.

4. Composition according to claim 3 which additionally comprises other vitamins.

5. Composition according to claim 1 which additionally comprises suitable salts of Mg, Ca, K, and Fe.

6. Composition according to claim 1 which additionally comprises trace elements.

7. Composition according to claim 1 comprising ascorbic acid or ascorbate and quercetin-3-o-glucoside (isoquercetin) in a molar ratio in the range of 2 : 1 to 1 : 2.

8. Composition according to claim 1 comprising ascorbic acid or ascorbate and quercetin-3-o-glucoside (isoquercetin) in a molar ratio of about 1 : 1.

9. Composition according to claim 1 in the form of a dosage unit, comprising 30 - 1500 mg ascorbic acid or ascorbate.

10. A method of using the composition according to claim 1 which comprises employing the composition of claim 1 as a food supplement.

11. Method of maintaining long biological activity and high concentrations of ascorbate and isoquercetin in human organs, skin, tissues and cells which comprises orally administering a composition according to claim 1.

12. Method of protection against oxidative damage to organs, skin, tissues and cells which comprises orally administering a composition according to claim 1.

13. Method of prevention of arteriosclerosis, cardiovascular diseases, allergic and inflammatory disorders, bacterial and viral infections, metabolic dysfunctions, and of other pathologic conditions involving oxidative damage which comprises orally administering a composition according to claim 1.

14. Method of supporting a pharmacological treatment of a disease or dysfunction caused by oxidative damage which comprises orally administering a composition according to claim 1.

15. Pharmaceutical composition containing a pharmaceutically active ingredient, a pharmaceutically acceptable carrier and a composition according to claim 1.

16. In a food supplement comprising ascorbic acid, ascorbate, or a derivative of ascorbic acid or ascorbate that would yield ascorbate, or semidehydroascorbic acid, or dehydroascorbic acid in vivo, the improvement comprising incorporating one or more derivatives of quercetin selected from the group consisting of quercetin-3-O-glucoside (isoquercetin) quercetin-4'-glucoside, quercetin-3'-glucoside, and quercetin-7-glucoside.

## ABSTRACT OF THE DISCLOSURE

The present invention relates to compositions comprising ascorbic acid and derivatives of quercetin with an increased bioavailability of ascorbic acid. These compositions are useful as food supplements possessing preventive properties against damage to human organs, including skin, tissues and cells due to oxidative stress or damage.

U.S. DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

*THIS IS TO CERTIFY that page (s)* Declaration *is missing from the U.S. Patent and Trademark Office microform records.*

H. L. Jackson
*Certifying Officer*

AUG 17 1999
*DATE*

**This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record**

# BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: ______________________

**IMAGES ARE BEST AVAILABLE COPY.**
**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**